(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079156 A1

(51) International Patent Classification[7]: C07D 211/58, 401/12, 405/12, 413/12, 417/12, A61K 31/4468, 31/4523, A61P 11/00, 17/00, 29/00, 37/00

(21) International Application Number: PCT/SE02/00598

(22) International Filing Date: 26 March 2002 (26.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0108046.4 30 March 2001 (30.03.2001) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/079156 A1

(54) Title: NOVEL PIPERIDINE DERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR

(57) Abstract: The invention provides a compound of formula (I) wherein: R^1 is a group selected from: (a), (b) and (c) or a pharmaceutically acceptable salt thereof or a solvate thereof; compositions containing these compounds, processes for preparing them and their use as modulators of chemokine activity (especially CCR5 activity).

NOVEL PIPERIDINE DERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in EP-A1-1013276, WO00/08013, WO99/38514 and WO99/04794. Piperidine oxime derivatives are disclosed in GB1538542.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

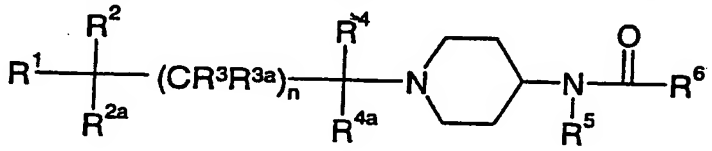
Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1a and MIP-1b and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

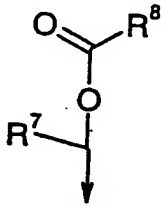
The present invention provides a compound of formula (I):

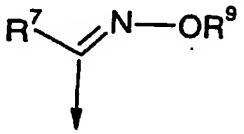


(I)

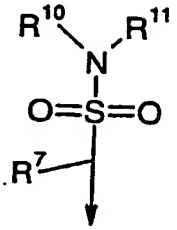
wherein:

R^1 is a group selected from:





and



R^2, R^{2a}, R^4 and R^{4a} are, independently, hydrogen or C_{1-4} alkyl;

R^3 and R^{3a} are, independently, hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

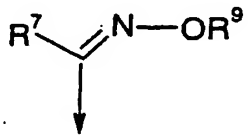
n is 0 or 1;

R^5 is hydrogen, C_{1-4} alkyl (optionally substituted by halogen, hydroxy, C_{1-4} alkoxy, C_{3-7} cycloalkyl, SH, C_{1-4} alkylthio, cyano or $S(O)_q(C_{1-4}$ alkyl)), C_{3-4} alkenyl, C_{3-4} alkynyl or C_{3-7} cycloalkyl;

R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH;

R^7 is phenyl, heteroaryl, phenyl(C_{1-4} alkyl) or heteroaryl(C_{1-4} alkyl);

R^8 is C_{1-8} alkyl, OR^{12}, $NR^{13}R^{14}$, phenyl, heteroaryl, phenyl(C_{1-2})alkyl or heteroaryl(C_{1-2})alkyl;
R^9, R^{10} and R^{11} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy, phenyl or heteroaryl), phenyl or heteroaryl; or R^{10} and R^{11} may join to form a 5- or 6-membered ring which may additionally include an oxygen atom or a further nitrogen atom, said ring being optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl);
R^{12} and R^{13} are C_{1-8} alkyl (optionally substituted by halogen, OH, cyano, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, $NR^{15}R^{16}$, C(O)NH(OH), NHC(O)(C_{1-4} alkyl), heterocyclyl, phenyl or heteroaryl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl (optionally substituted by C_{1-6} alkyl), phenyl, heteroaryl or heterocyclyl;
R^{14} is hydrogen or is independently selected from the list of options recited for R^{13};
or R^{13} and R^{14} join to form a 5, 6, 7 or 8-membered monocyclic or bicyclic ring system which is optionally unsaturated, optionally includes a further nitrogen atom or also includes an oxygen or sulphur atom, and which is optionally substituted by OH, C_{1-6} alkyl or C_{1-6} hydroxyalkyl;
R^{15} and R^{16} are, independently, hydrogen or C_{1-6} alkyl;
wherein the phenyl, heteroaryl and heterocyclyl rings of any of the foregoing are independently optionally substituted by halo, cyano, nitro, oxo, hydroxy, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^{17}R^{18}$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), C(O)(C_{1-4} alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3;
R^{17} and R^{18} are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl);
m, p and q are, independently, 0, 1 or 2;
or a pharmaceutically acceptable salt thereof or a solvate thereof;
provided that when R^1 is



n is 0 or 1; R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^9 are all hydrogen; and R^6 is unsubstituted phenyl; then R^7 is not optionally substituted phenyl, or a salt thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl or iso-propyl.

Alkenyl and alkynyl groups and moieties are, for example, vinyl, allyl or propargyl.

Cycloalkyl is a mono-, bi- or tri-cyclic structure such as, for example, cyclopropyl, cyclopentyl, cyclohexyl or adamantyl.

Cycloalkenyl comprises one double bond and is, for example, cyclopentenyl or cyclohexenyl.

Acyl is, for example, carbonyl substituted by C_{1-6} alkyl or optionally substituted phenyl.

Heterocyclyl is a non-aromatic 3, 4, 5 or 6 membered ring comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heterocyclyl is, for example, aziridinyl, azetidinyl, oxetanyl, piperidinyl, 4,5-dihydro-oxazolyl, 4,5-dihydroimidazolyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperazinyl or tetrahydrofuryl.

Heteroaryl is an aromatic 5 or 6 membered ring comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heteroaryl is, for example, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, quinazolinyl, quinoxalinyl, indolyl, isoindolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, benzthiazolyl or cinnolinyl.

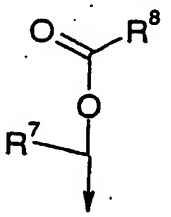
Phenylalkyl is, for example, benzyl, 1-(phenyl)ethyl or 2-(phenyl)ethyl.

Heteroarylalkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or 2-(pyridinyl)ethyl.

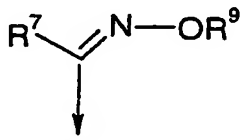
The group $S(O)_2NR^{17}R^{18}$ is, for example, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, $S(O)_2$(4-C(O)H-piperazin-1-yl) or $S(O)_2$(4-$C(O)CH_3$-piperazin-1-yl).

Phenyl(C_{1-2} alkyl)NH is, for example, benzylamino. Heteroaryl(C_{1-2} alkyl)NH is, for example, pyridinylCH_2NH, pyrimidinylCH_2NH or pyridinyl$CH(CH_3)NH$.

In one aspect R^1 is a group selected from:



and



In a further aspect R^1 is $CHR^7OC(O)NR^{13}R^{14}$ wherein R^{13} and R^{14} are as defined above. In yet another aspect R^{14} is not hydrogen. In a further aspect R^{13} and R^{14} join to form a ring system as defined above.

In a still further aspect n is 0.

In yet another aspect R^4 and R^{4a} are hydrogen or methyl; for example R^4 is hydrogen and R^{4a} is hydrogen or methyl.

In a further aspect R^4 is hydrogen, R^{4a} is hydrogen or methyl, and R^3 and R^{3a} are both hydrogen.

In a still further aspect n is 0 and R^2, R^{2a}, R^4 and R^{4a} are all hydrogen; R^{4a} can also be methyl.

In another aspect n is 1 and R^2, R^{2a}, R^3, R^{3a}, R^4 and R^{4a} are all hydrogen; R^{4a} can also be methyl.

In yet another aspect R^5 is hydrogen or C_{1-4} alkyl (such as methyl, ethyl or iso-propyl), C_{3-4} alkenyl (for example allyl), C_{3-4} alkynyl (for example propargyl), C_{3-7} cycloalkyl (for example cyclopropyl) or C_{3-7} cycloalkyl(C_{1-4} alkyl) (for example cyclopropylCH_2). The variable R^5 can be methyl, ethyl or allyl. It is preferred that R^5 is ethyl.

In a further aspect R^6 is preferably optionally substituted benzyl, especially benzyl singly substituted (such as in the 4-position) by $S(O)_2(C_{1-4})$alkyl (such as $S(O)_2CH_3$) or $S(O)_2NR^9R^{10}$ {R^9 and R^{10} are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl)} (such as $S(O)_2NH_2$, $S(O)_2NH(CH_3)$, $S(O)_2N(CH_3)_2$, $S(O)_2$(4-C(O)H-piperazin-1-yl) or $S(O)_2$(4-C(O)CH_3-piperazin-1-yl).

In a still further aspect R^6 is preferably optionally substituted benzyl, especially benzyl singly substituted (such as in the 4-position) by halo (such as fluoro) or $S(O)_2(C_{1-4})$alkyl (such as $S(O)_2CH_3$).

In another aspect R^7 is optionally substituted phenyl (especially optionally substituted by halo, cyano, methyl, ethyl, methoxy, ethoxy, NH_2, $NHCH_3$, $N(CH_3)_2$, CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3). In another aspect R^7 is optionally substituted phenyl (especially optionally substituted by halogen or CF_3). For example R^7 is unsubstituted phenyl, 3-fluorophenyl, 3-chlorophenyl, 4-fluorophenyl or 4-CF_3-phenyl.

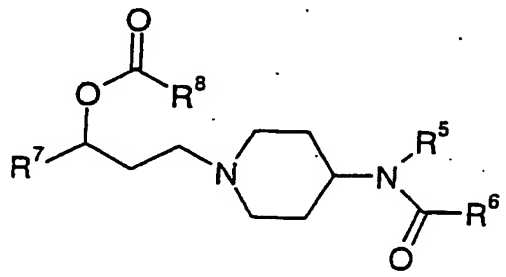
In yet another aspect R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, $NR^{13}R^{14}$, C_{3-7} cycloalkyl (optionally substituted by C_{1-4} alkyl) or heteroaryl; R^{13} is C_{1-8} alkyl (optionally substituted by halogen, cyano, hydroxy, NH_2, $N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, C_{1-4} thioalkyl, C_{3-7} cycloalkyl, heterocyclyl, phenyl, heteroaryl, $NHC(O)(C_{1-4}$ alkyl) or C(O)NHOH), C_{3-6} alkenyl, C_{3-6} alkynyl, phenyl or heteroaryl; R^{14} is hydrogen, C_{1-8} alkyl (optionally substituted by cyano or hydroxy) or C_{3-6} alkenyl; or R^{13} and R^{14} together with the nitrogen to which hey are attached form a oxiranyl, pyrrolidinyl, piperidinyl, morpholinyl, dihydropyrrolyl, tetrahydropyridinyl, piperazinyl, thiomorpholinyl, homopiperazinyl or homopiperidinyl ring all of which are optionally substituted by hydroxy, C_{1-4} alkyl or C_{1-4} hydroxyalkyl; wherein phenyl is optionally substituted by halogen, cyano, hydroxy or C_{1-6} alkyl; and heteroaryl is optionally substituted by oxo, halogen, cyano, hydroxy or C_{1-6} alkyl.

In a further aspect R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, $NR^{13}R^{14}$, C_{3-7} cycloalkyl (optionally substituted by C_{1-4} alkyl) or heteroaryl; R^{13} is C_{1-8} alkyl (optionally substituted by halogen, cyano, hydroxy, NH_2, $N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, C_{1-4} thioalkyl, C_{3-7} cycloalkyl, heterocyclyl, phenyl, heteroaryl, $NHC(O)(C_{1-4}$ alkyl) or C(O)NHOH), C_{3-6} alkenyl, C_{3-6} alkynyl, phenyl or heteroaryl; and R^{14} is hydrogen, C_{1-8} alkyl (optionally substituted by cyano or hydroxy) or C_{3-6} alkenyl.

In a still further aspect R^9 is C_{1-4} alkyl (such as ethyl) or C_{3-4} alkenyl (such as allyl).

In yet another aspect R^{10} and R^{11} are, independently, hydrogen or C_{1-4} alkyl (such as methyl).

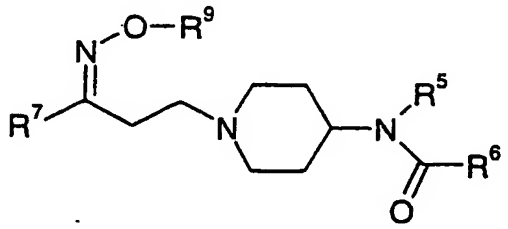
In one aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein R^5, R^6, R^7 and R^8 are as hereinbefore defined.

In one aspect the present invention provides a compound of formula (Ib):



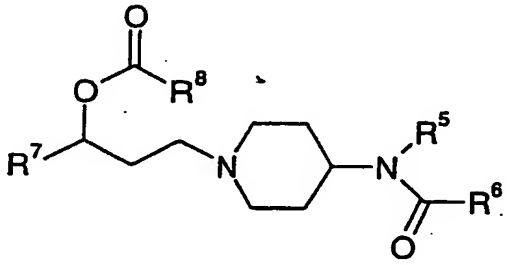
(Ib)

wherein R^5, R^6, R^7 and R^9 are as hereinbefore defined, provided that when R^5 and R^9 are both hydrogen; and R^6 is unsubstituted phenyl; then R^7 is not optionally substituted phenyl, or a salt thereof.

The following compounds illustrate the invention.

TABLE I

All compounds in Table I are of formula (Ia) below.



(Ia)

Compound No.	R^8	R^7	R^5	R^6	LCMS (MH+)
1	pyrrolidin-1-yl	Ph-4-F	Et	CH_2Ph-4-F	514
2	OCH_3	Ph-4-F	Et	CH_2Ph-4-SO_2Me	535
3	$N(CH_2CH_3)_2$	Ph-4-F	Et	CH_2Ph-4-F	516
4	$NH(CH_2)_2$(pyrrolidin-1-yl)	Ph	Et	CH_2Ph-4-SO_2Me	599
5	piperidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	570
6	$NHCH_2CF_3$	Ph	Et	CH_2Ph-4-SO_2Me	584
7	pyrrolidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	556
8	morpholin-4-yl	Ph	Et	CH_2Ph-4-SO_2Me	572
9	4-CH_3-piperazin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	585
10	$NHCH_2$Ph	Ph	Et	CH_2Ph-4-SO_2Me	592
11	$NHCH_2$Ph-4-F	Ph	Et	CH_2Ph-4-SO_2Me	610
12	$NH(CH_2)_2OMe$	Ph	Et	CH_2Ph-4-SO_2Me	560
13	N(Me)$(CH_2)_2$OMe	Ph	Et	CH_2Ph-4-SO_2Me	574

14	$NHCH_2$(pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	593
15	$NHCH_2$(pyridin-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	593
16	NH(cyclopropyl)	Ph	Et	CH_2Ph-4-SO_2Me	
17	NH(cyclobutyl)	Ph	Et	CH_2Ph-4-SO_2Me	
18	NH(cyclopentyl)	Ph	Et	CH_2Ph-4-SO_2Me	
19	NH(cyclohexyl)	Ph	Et	CH_2Ph-4-SO_2Me	
20	$N(CH_2CN)_2$	Ph	Et	CH_2Ph-4-SO_2Me	580
21	$N(CH_3)((CH_2)_2CN)$	Ph	Et	CH_2Ph-4-SO_2Me	569
22	$N(CH_3)((CH_2)_2OH)$	Ph	Et	CH_2Ph-4-SO_2Me	560
23	$N(CH_2CH_3)((CH_2)_2OH)$	Ph	Et	CH_2Ph-4-SO_2Me	574
24	$N(CH_2OH)_2$	Ph	Et	CH_2Ph-4-SO_2Me	590
25	NH(1,3,4-thiadiazol-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
26	NH(3-CH_3-isoxazol-5-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
27	NH(5-CH_3-isoxazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
28	NH(fur-2-yl-CH_2)	Ph	Et	CH_2Ph-4-SO_2Me	582
29	$NH(CCH_3(CH_2OH)_2)$	Ph	Et	CH_2Ph-4-SO_2Me	590
30	oxiran-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	
31	2,5-dihydropyrrol-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	
32	NH(1,2,4-1H-triazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
33	NH(1H-pyrazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	568
34	NH(1H-4-CN-pyrazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
35	NH(tetrahydrofuran-2-ylCH_2)	Ph	Et	CH_2Ph-4-SO_2Me	
36	1,2,3,6-tetrahydropyridin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	
37	piperazin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	571
38	thiomorpholin-4-yl	Ph	Et	CH_2Ph-4-SO_2Me	588
39	4-OH-piperidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	586
40	4-CH_3-piperidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	584
41	NH(pyrimidin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	580
42	NH(4-CH_3-pyrimidin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
43	NH(pyrimidin-4-yl)	Ph	Et	CH_2Ph-4-SO_2Me	580
44	NH(pyridazin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	

45	NCH_3(pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
46	NH(pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	579
47	NH(3-OH-pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	595
48	NH(3-CH_3-pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	593
49	NH(4-CH_3-pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
50	NH(5-CH_3-pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
51	NH(pyridin-2-yl-CH_2)	Ph	Et	CH_2Ph-4-SO_2Me	593
52	NH(pyridin-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	579
53	NH(pyridin-3-yl-CH_2)	Ph	Et	CH_2Ph-4-SO_2Me	593
54	NH(pyridin-4-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
55	NH(pyridin-4-yl-CH_2)	Ph	Et	CH_2Ph-4-SO_2Me	593
56	NH(1,2,4-triazin-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	581
57	homopiperazin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	585
58	homopiperidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	583
59	NH-phenyl	Ph	Et	CH_2Ph-4-SO_2Me	578
60	NH(2-OH-C_6H_4)	Ph	Et	CH_2Ph-4-SO_2Me	
61	NH(2-CH_3-C_6H_4)	Ph	Et	CH_2Ph-4-SO_2Me	592
62	NH(3-OH-C_6H_4)	Ph	Et	CH_2Ph-4-SO_2Me	
63	NH(3-CH_3-C_6H_4)	Ph	Et	CH_2Ph-4-SO_2Me	592
64	NH(4-OH-C_6H_4)	Ph	Et	CH_2Ph-4-SO_2Me	594
65	NH(3-CH_3-C_6H_4)	Ph	Et	CH_2Ph-4-SO_2Me	592
66	$NHC(CH_3)_2CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	574
67	$NHCH_2C(CH_3)_2NH_2$	Ph	Et	CH_2Ph-4-SO_2Me	573
68	$NHC(CH_3)_2CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	572
69	$NHCH(CH_3)CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
70	$NHCH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
71	$NHCH(CH_3)CH_2OCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
72	$NHCH(CH_3)CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	560
73	$NHCH(CH_3)CH_2CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	586
74	$NHCH(CH_3)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
75	$NHCH(CH_2OH)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574

76	$NHCH(CH_2CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
77	$NHCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	516
78	$NHCH_2CF_3$	Ph	Et	CH_2Ph-4-SO_2Me	
79	$NHCH_2C(CH_3)_3$	Ph	Et	CH_2Ph-4-SO_2Me	572
80	$NHCH_2CH(OCH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
81	$NHCH_2CH(OH)CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	560
82	$NHCH_2CH(OH)CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	576
83	$NHCH_2CH(OH)CH_2NH_2$	Ph	Et	CH_2Ph-4-SO_2Me	575
84	$NHCH_2CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
85	$NHCH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
86	$NH(CH_2)_2NHC(O)CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	587
87	$N(CH_3)(CH_2)_2NH_2$	Ph	Et	CH_2Ph-4-SO_2Me	559
88	$N(CH_2CH_3)(CH_2)_2NH_2$	Ph	Et	CH_2Ph-4-SO_2Me	573
89	$N((CH_2)_2OH)(CH_2)_2NH_2$	Ph	Et	CH_2Ph-4-SO_2Me	589
90	$N((CH_2)_2CH_3)(CH_2)_2NH_2$	Ph	Et	CH_2Ph-4-SO_2Me	
91	$NH(CH_2)_2N(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	573
92	$NH(CH_2)_2OCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	560
93	$NH(CH_2)_2O(CH_2)_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	590
94	$NH(CH_2)_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	546
95	$NHCH_2C{\equiv}CH$	Ph	Et	CH_2Ph-4-SO_2Me	
96	$NH(CH_2)_2C(CH_3)_3$	Ph	Et	CH_2Ph-4-SO_2Me	586
97	$NH(CH_2)_2CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	572
98	$NH(CH_2)_3N(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	587
99	$NH(CH_2)_3OCH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
100	$NH(CH_2)_3OH$	Ph	Et	CH_2Ph-4-SO_2Me	560
101	$NH(CH_2)_4OH$	Ph	Et	CH_2Ph-4-SO_2Me	574
102	$NH(CH_2)_4CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	572
103	$NH(CH_2)_5OH$	Ph	Et	CH_2Ph-4-SO_2Me	588
104	$NH(CH_2)_5CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
105	$N(CH_3)$phenyl	Ph	Et	CH_2Ph-4-SO_2Me	
106	$N(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	

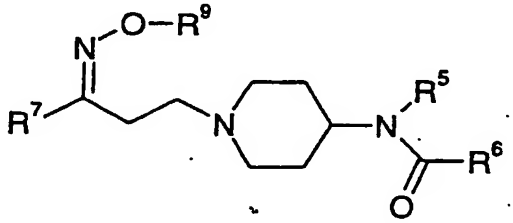
107	$N(CH_3)CH_2C{\equiv}CH$	Ph	Et	CH_2Ph-4-SO_2Me	
108	$N(CH_3)CH_2CH{=}CH_2$	Ph	Et	CH_2Ph-4-SO_2Me	
109	$N(CH_2CH{=}CH_2)_2$	Ph	Et	CH_2Ph-4-SO_2Me	582
110	$N(CH(CH_3)_2)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
111	$N(CH_3)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
112	$N(CH_3)(CH_2)_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	558
113	$N((CH_2)_2CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	586
114	$N(CH_3)(CH_2)_3CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	572
115	$N(CH_2CH_3)(CH_2)_3CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	586
116	$NH(CH_2)_3CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	580
117	3-OH-piperidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	586
118	$NH(CH_2)_2CN$	Ph	Et	CH_2Ph-4-SO_2Me	
119	$NH(CH_2)_2SCH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
120	$NH(CH_2)_3OCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
121	$N(CH_3)CH_2CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	572
122	$N(CH_2CH_3)CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
123	$N(CH_2CH_3)(CH_2)_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
124	NH(5-OH-1H-pyrazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
125	NH(1,3,5-triazin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
126	$NHCH_2CH(CH_3)(CH_2)_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	586
127	$NH(CH_2)_2OCH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
128	$NHCH_2$cyclopropyl	Ph	Et	CH_2Ph-4-SO_2Me	556
129	NH(isoxazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
130	NH(6-OH-pyridin-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	595
131	$NH(CH_2)_3SCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	
132	$N(CH_3)C(CH_3)_3$	Ph	Et	CH_2Ph-4-SO_2Me	
133	$N(CH_3)CH(CH_3)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	572
134	$NHCH_2C(=CH_2)CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	556
135	$NHCH_2CH(OH)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
136	$NHCH_2C(CH_3)_2CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	588
137	$NHCH(CH_2OH)CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	588

138	(*R*)-2-CH_2OH-pyrrolidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	586
138	NH(3-oxo-isoxazolidin-4-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
140	$NHCH(CH_3)CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	560
141	$NHCH(CH_3)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	558
142	$NHCH(CH_2OH)CH_2CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
143	(*R*)-$NHCH_2CH(OH)CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	560
144	(*S*)-$NHCH_2CH(OH)CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	560
145	NH(1-CH_3-pyrazol-5-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
146	NH(1H-5-CH_3-pyrazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
147	$NHCH_2CN$	Ph	Et	CH_2Ph-4-SO_2Me	
148	NH(4-CH_3-oxazol-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
149	$N(CH_3)(CH_2)_2OCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
150	NH(1H-tetrazol-5-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
151	$NHCH_2C(O)NHOH$	Ph	Et	CH_2Ph-4-SO_2Me	575
152	(*S*)-$NHCH_2CH(OH)CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	576
153	(*R*)-$NHCH_2CH(OH)CH_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	576
154	$NHC(CH_3)_2(CH_2)_2OH$	Ph	Et	CH_2Ph-4-SO_2Me	588
155	$NHCH_2C(CH_3)_2OCH_3$	Ph	Et	CH_2Ph-4-SO_2Me	588
156	$NHCH(CH_2OH)CH(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
157	2-azabicyclo[2.2.1]heptan-2-yl	Ph	Et	CH_2Ph-4-SO_2Me	582
158	$NHCH_2$(1H-imidazol-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	582
159	(*S*)-3-CH_3-piperazin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	
160	(*R*)-3-CH_3-piperazin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	585
161	(*R*)-$NHCH_2$(tetrahydrofuran-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	586
162	$N(CH_3)$(pyridin-4-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
163	$N(CH_3)C(CH_3)_2CN$	Ph	Et	CH_2Ph-4-SO_2Me	
164	$NH(CH_2)_2CH(OH)CH_3$	Ph	Et	CH_2Ph-4-SO_2Me	574
165	NH(4-CN-isoxazol-3-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
166	NH(3-CH_3-cyclopentyl)	Ph	Et	CH_2Ph-4-SO_2Me	584
167	(*S*)-3-OH-pyrrolidin-1-yl	Ph	Et	CH_2Ph-4-SO_2Me	

168	NH(1H-3-CH_3-pyrazol-5-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
169	NHCH(CH_3)$CH_2N(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
170	$NHCH_2CH(CH_3)N(CH_3)_2$	Ph	Et	CH_2Ph-4-SO_2Me	
171	(*S*)-$NHCH_2$(tetrahydrofuran-2-yl)	Ph	Et	CH_2Ph-4-SO_2Me	
172	$C(CH_3)_3$	Ph	Et	CH_2Ph-4-SO_2Me	543

TABLE II

All compounds in Table II are of formula (Ib) below.



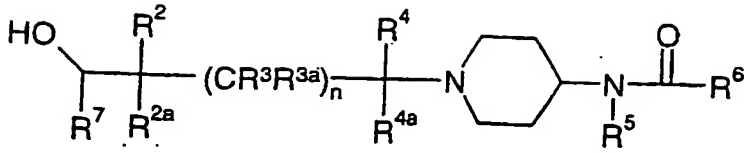
(Ib)

Compound No.	R^9	R^7	R^5	R^6	LCMS (MH+)
1	allyl	Ph	Et	CH_2Ph-4-SO_2Me	512
2	ethyl	Ph	Et	CH_2Ph-4-SO_2Me	500

Ph = phenyl; Et = ethyl

The compounds of formula (I), (Ia) and (Ib), where R^2, R^{2a}, R^4 and R^{4a} and, if present, R^3 and R^{3a} are all hydrogen, can be prepared as shown in Schemes 1 and 2 below, or by adaptation of known methods described in the art. Compounds wherein one or more of R^2, R^{2a}, R^4 and R^{4a} and, if present, R^3 and R^{3a} are hydrogen can be prepared by methods analogous to those shown in Schemes 1 and 2, by changing one or more reactants in the methods of Schemes 1 or 2, or by adaptation of known methods described in the art. In a further aspect the invention provides processes for preparing the compounds of formula (I), (Ia) and (Ib). Many of the intermediates in the processes are novel and these are provided as further features of the invention. Compounds of formula (I) wherein R^1 is $CHR^7S(O)_2NR^{10}R^{11}$ can be made by routine adaptation of methods herein described combined with methods described in the literature.

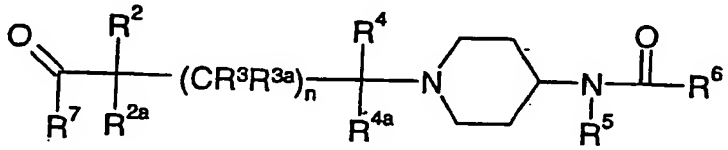
Thus, a compound of formula (I) wherein R^1 is $CHR^7OC(O)R^8$ can be prepared by reacting a compound of formula (II):



(II)

with a compound of formula $R^8C(O)Cl$ in the presence of a suitable base (such as a tertiary amine, for example of formula $R^aR^bR^cN$, where R^a, R^b and R^c are, independently, C_{1-6} alkyl; for example triethylamine) and in a suitable solvent (such as dichloromethane) at a temperature in the range 10-50°C. Alternatively, a compound of formula (II) is pre-treated with sodium hydride in a suitable solvent (for example N-methylpyrrolidone) and the compound of formula $R^8C(O)Cl$ added to this mixture.

A compound of formula (I) wherein R^1 is $CR^7{=}NOR^9$ can be prepared by reacting a compound of formula (III):



(III)

(as a free base or in salt form, for example, in the form of a hydrochloride) with a compound of formula R^9ONH_2 (preferably in salt form, for example in the form of a hydrochloride) in a suitable solvent (such as dichloromethane) at a temperature in the range 10-50°C.

A compound of formula (I) wherein R^1 is $CHR^7OC(O)NHR^{13}$ can be prepared by reacting a compound of formula (II) with a compound of formula $R^{13}NCO$.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)). Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); pulmonary fibrosis; asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis;

seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, inhibiting the entry of viruses into target cells, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura, disorders of the menstrual cycle, glomerulonephritis or cerebral malaria.

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

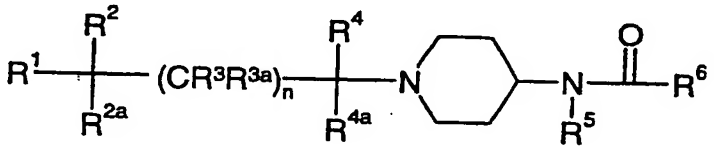
According to a further feature of the present invention there is provided a method for

modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state, such as rheumatoid arthritis) in a warm blooded animal (such as man) suffering from, or at risk of, said disease, which comprises administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or solvate thereof.

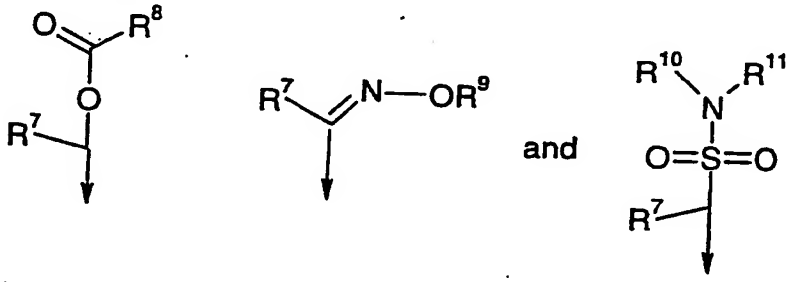
The invention also provides a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in therapy (including prophylaxis); for example in the treatment of a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, such as in the treatment of rheumatoid arthritis.

The invention also provides a compound of the formula (I):



(I)

wherein: R^1 is a group selected from:



R^2, R^{2a}, R^4 and R^{4a} are, independently, hydrogen or C_{1-4} alkyl;

R^3 and R^{3a} are, independently, hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

n is 0 or 1;

R^5 is hydrogen, C_{1-4} alkyl (optionally substituted by halogen, hydroxy, C_{1-4} alkoxy, C_{3-7} cycloalkyl, SH, C_{1-4} alkylthio, cyano or $S(O)_q(C_{1-4}$ alkyl)), C_{3-4} alkenyl, C_{3-4} alkynyl or C_{3-7} cycloalkyl;

R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH;

R^7 is phenyl, heteroaryl, phenyl(C_{1-4} alkyl) or heteroaryl(C_{1-4} alkyl);

R^8 is C_{1-8} alkyl, OR^{12}, $NR^{13}R^{14}$, phenyl, heteroaryl, phenyl(C_{1-2})alkyl or heteroaryl(C_{1-2})alkyl;

R^9, R^{10} and R^{11} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy, phenyl or heteroaryl), phenyl or heteroaryl; or R^{10} and R^{11} may join to form a 5- or 6-membered ring which may additionally include an oxygen atom or a further nitrogen atom, said ring being optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl);

R^{12} and R^{13} are C_{1-8} alkyl (optionally substituted by halogen, OH, cyano, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, $NR^{15}R^{16}$, C(O)NH(OH), NHC(O)(C_{1-4} alkyl), heterocyclyl, phenyl or heteroaryl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl (optionally substituted by C_{1-6} alkyl), phenyl, heteroaryl or heterocyclyl;

R^{14} is hydrogen or is independently selected from the list of options recited for R^{13};

or R^{13} and R^{14} join to form a 5, 6, 7 or 8-membered monocyclic or bicyclic ring system which is optionally unsaturated, optionally includes a further nitrogen atom or also includes an oxygen or sulphur atom, and which is optionally substituted by OH, C_{1-6} alkyl or C_{1-6} hydroxyalkyl;

R^{15} and R^{16} are, independently, hydrogen or C_{1-6} alkyl;

wherein the phenyl, heteroaryl and heterocyclyl rings of any of the foregoing are independently optionally substituted by halo, cyano, nitro, oxo, hydroxy, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^{17}R^{18}$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), C(O)(C_{1-4} alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3;

R^{17} and R^{18} are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl);

m, p and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof; for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

The invention further provides a compound of the formula (Ia), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In a further aspect the invention provides a compound of formula (Ib) wherein R^5, R^6,

R^7 and R^9 are as defined immediately above, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example in modulating chemokine receptor activity (especially CCR5 receptor activity (especially in the treatment of rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (Ia) and (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (Ia) and (Ib), or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30

mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Clamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where

values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

(xi) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;
DIPEA	*N*,*N*-diisopropylethylamine;
NMP	*N*-methylpyrrolidinone;
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
THF	tetrahydrofuran;
EtOH	ethanol; and
EtOAc	ethyl acetate.

EXAMPLE 1

This Example illustrates the preparation of *N*-[1-(3-[4-fluorophenyl]-3-[1-pyrrolidinylcarbonyloxy]propyl)-4-piperidinyl]-*N*-ethyl-4-fluorophenylacetamide (Compound No. 1 of Table I).

To a stirred solution of *N*-[1-(3-[4-fluorophenyl]-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-fluorophenylacetamide (Method 1) (101mg, 0.24mmol) in NMP (2mL) was added sodium hydride (20mg 60% dispersion, 0.48mmol) and the resulting mixture was stirred at room temperature for 10min. 1-Pyrrolidinecarbonyl chloride (35mg, 0.26mmol) was added and the resulting mixture stirred at room temperature for 20h. The mixture was partitioned between water and ethyl acetate. The aqueous phase was evaporated and the residue triturated with diethyl ether to yield the title compound as a solid (110mg, 89%); NMR (DMSO at 373K): 1.09 (t, 3H), 1.47 (m, 2H), 1.71 (m, 2H), 1.75-3.05 (m, 6H), 3.32 (m, 12H), 3.70 (s, 2H), 3.84 (br m, 1H), 5.68 (t, 1H), 7.10 (m, 4H), 7.27 (m, 2H) and 7.39 (m, 2H); MS: 514.

The same method was used for Compound No. 3 of Table I:

NMR ($CDCl_3$): 0.95-1.25 (br m, 9H), 1.80 (br m, 2H), 2.01 (m, 2H), 2.26 (m, 2H), 2.94 (br m, 2H), 3.26 (m, 6H), 3.37 (t, 2H), 3.50 and 4.40 (m, 1H), 3.66 and 3.69 (s, 2H), 5.70 (m, 1H), 7.00 (m, 4H) and 7.25 (m, 4H); MS: 516.

EXAMPLE 2

This Example illustrates the preparation of *N*-[1-(3-[4-fluorophenyl]-3-methoxycarbonyloxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonyl-phenylacetamide hydrochloride (Compound No. 2 of Table I).

To a solution of *N*-[1-(3-[4-fluorophenyl]-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 11) (230mg, 0.48mmol) in DCM (5mL) was added 4-nitrophenylchloroformate (101mg, 0.50mmol) and triethylamine (80μL, 0.50mmol) and the resulting mixture stirred at room temperature for 30min. The mixture applied to an ISOLUTE™ SCX column (10g) which was then washed with DCM followed by MeOH. The crude product was triturated with ethereal HCl/iso-hexane to yield the title compound as a solid (180mg, 70%); NMR ($CDCl_3$): 0.85 (m, 3H), 1.05-1.95 (m, 6H), 2.02 (m, 1H), 2.16 (m, 1H), 2.30 (m, 2H), 2.83 (m, 1H), 2.96 (m, 1H), 3.02 (s, 3H), 3.32 (q, 2H), 3.50 and 4.28 (m, 1H), 3.72 (s, 3H), 3.77 and 3.79 (2s, 2H), 5.62 (t, 3H), 7.03 (m, 2H), 7.32 (m, 2H), 7.45 (m, 2H) and 7.90 (d, 2H); MS: 535.

EXAMPLE 3

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[2-pyrrolidin-1-ylethylaminocarbonyloxy]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 4 of Table I).

A solution of *N*-[1-(3-phenyl-3-[4-nitrophenoxycarbonyloxy]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 3) (0.25g, 0.40mmol) in DCM (2mL) was added to 1-(2-aminoethyl)pyrrolidine (127μL, 1.0mmol) and the resulting mixture stirred at room temperature for 16h. The mixture was partitioned between DCM (5mL) and saturated aqueous sodium bicarbonate solution (5mL). The organic phase was applied to an ISOLUTE™ SCX column (10g) which was then washed with DCM followed by MeOH followed by 4% ammonia/MeOH to give the title compound (180mg, 75%); NMR ($CDCl_3$): 0.86 and 0.88 (t, 3H), 1.15 (m, 2H), 1.25 (m, 2H), 1.30-2.20 (m, 8H), 2.32 (m, 2H), 2.49 (m, 4H), 2.57 (m, 2H), 2.87 (m, 1H), 2.97 (m, 1H), 3.03 (s, 3H), 3.29 (m, 4H), 3.50 and 4.20 (m, 1H), 3.78 and 3.79 (s, 2H), 5.22 (m, 1H), 5.71 (m, 1H), 7.28 (m, 1H), 7.33 (m, 4H), 7.44 (d, 2H) and 7.90 (d, 2H); MS: 599.

The same method was used for Compound No. 117 of Table I:
NMR (DMSO at 373K): 1.14 (t, 3H), 1.38 (m, 2H), 1.53 (m, 2H), 1.60-2.10 (m, 8H), 2.33 (m, 2H), 2.75-3.05 (m, 6H), 3.15 (s, 3H), 3.31 (m, 2H), 3.47 (br m, 1H), 3.65 (m, 1H), 3.81 (m,

1H), 3.83 (s, 2H), 4.47 (br m, 1H), 5.68 (m, 1H), 7.28 (m, 1H), 7.33 (m, 4H), 7.51 (d, 2H) and 7.85 (d, 2H); MS: 586.

The same method was used for Compound No. 136 of Table I:

NMR (CDCl3): 0.86 and 0.93 (2s, 6H), 1.16 and 1.27 (2t, 3H), 1.35-2.20 (m, 9H), 2.32 (q, 2H), 2.80-3.50 (m, 11H), 3.78 and 3.80 (2s, 2H), 4.40 (m, 1H), 5.05 (m, 1H), 5.70 (m, 1H), 7.32 (m, 5H), 7.46 (m, 2H) and 7.91 (m, 2H); MS: 588.

EXAMPLE 4

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[*tert*-butylcarbonyloxy]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 172 of Table I).

To a solution of *N*-[1-(3-phenyl-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 4) (150mg, 0.33mmol) in DCM (2mL) was added trimethylacetyl chloride (44µL, 0.36mmol) and triethylamine (50µL, 0.36mmol) and the resulting mixture was stirred at 40°C for 16h then allowed to cool. The mixture was partitioned between DCM and water, the organic phase was washed with brine, dried (Na_2SO_4) and evaporated giving the title compound (141mg, 79%); NMR: 1.02 and 1.15 (t, 3H), 1.16 (s, 9H), 1.46 (m, 2H), 1.66 (m, 2H), 1.89 (m, 2H), 2.26 (m, 2H), 2.83 (m, 2H), 3.20 (m, 4H), 3.30 (m, 6H), 3.65 and 4.09 (m, 1H), 3.81 and 3.87 (2s, 2H), 5.69(m, 1H), 7.33 (m, 5H), 7.59 (d, 2H) and 7.85 (d, 2H); MS: 543.

EXAMPLE 5

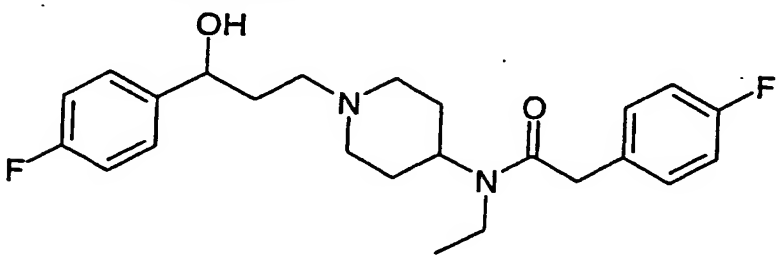
This Example illustrates the preparation of *N*-[1-(3-phenyl-3-allyloxyiminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 1 of Table II).

To a solution of *N*-[1-(3-phenyl-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Method 5) (500mg, 1mmol) in DCM (10mL) was added *O*-allyl hydroxylamine hydrochloride (131mg, 1.2mmol) followed by sodium sulphate (2g). The resulting mixture was stirred at reflux for 20h then allowed to cool. The mixture was filtered and the filtrate diluted with DCM, washed with water and brine, dried (Na_2SO_4) and concentrated to afford the title compound as a solid (400mg, 78%); NMR ($CDCl_3$): 1.29 (m, 3H), 1.87 (m, 2H), 2.64 (m, 2H), 2.82 (m, 2H), 3.03 (s, 3H), 3.14 (m, 1H), 3.41 (m, 2H), 3.65 (m, 2H), 3.78 (s, 2H), 4.70 (d, 2H), 5.27 (m, 2H), 5.29 (s, 2H), 6.00 (m, 1H), 7.41 (m, 5H), 7.74 (m, 2H) and 7.88 (m, 2H); MS: 512.

Methods

Method 1

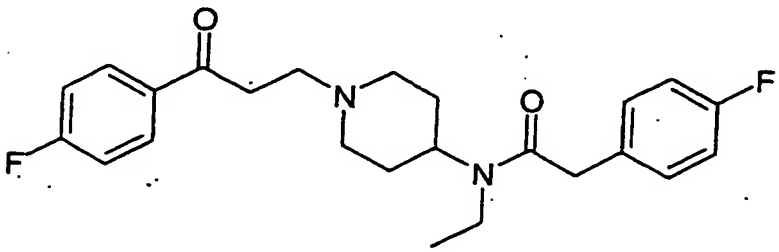
Preparation of *N*-[1-(3-[4-fluorophenyl]-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-fluorophenylacetamide



To a solution of *N*-[1-(3-[4-fluorophenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-fluorophenylacetamide (Method 2) (8.7mmol) in methanol (100mL) was added sodium borohydride (0.66g, 17.4mmol). The resulting mixture was stirred at room temperature for 20h. Water (5mL) was added and the mixture evaporated. The residue was purified by silica column chromatography (gradient elution from ethyl acetate to 50% ethyl acetate/MeOH) to give the title compound (2.77g, 76%): NMR ($CDCl_3$): 0.85 and 1.12 (t, 3H), 1.21 (m, 2H), 1.45 (m, 1H), 1.55-1.90 (m, 3H), 1.98 (m, 1H), 2.22 (m, 1H), 2.56 (m, 1H), 2.63 (m, 1H), 3.12 (m, 2H), 3.27 (q, 2H), 3.58 and 4.49 (m, 1H), 3.67 and 3.71 (s, 2H), 4.88 (m, 1H), 7.00 (m, 4H), 7.22 (m, 2H), 7.31 (m, 2H); MS: 417.

Method 2

Preparation of *N*-[1-(3-[4-fluorophenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-fluorophenylacetamide

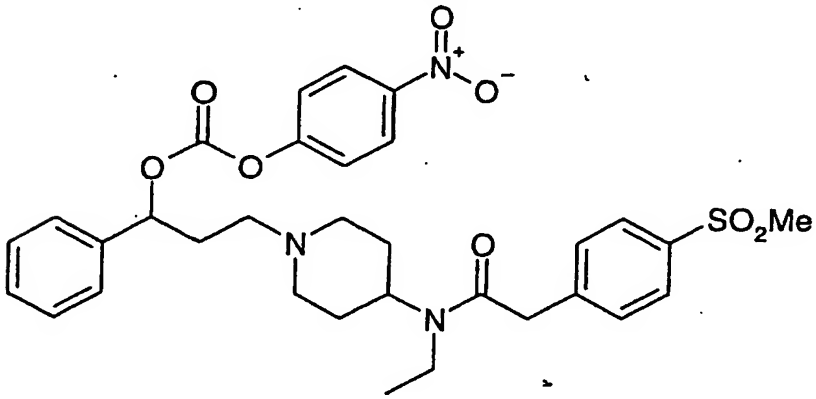


To a solution of *N*-(4-piperidinyl)-*N*-ethyl-4-fluorophenylacetamide (Method 9) (2.3g, 8.7mmol) in DMF (50mL) was added DIPEA (3mL, 17.4mmol) and 3-chloro-4'-fluoropropiophenone (1.7g, 9.1mmol). The resulting mixture was stirred at room temperature for 16h then partitioned between water and ethyl acetate. The organic phase was washed with

brine, dried (Na_2SO_4) and evaporated to give the title compound as an oil (~4g) which was used in the next reaction without further purification; MS: 415.

Method 3

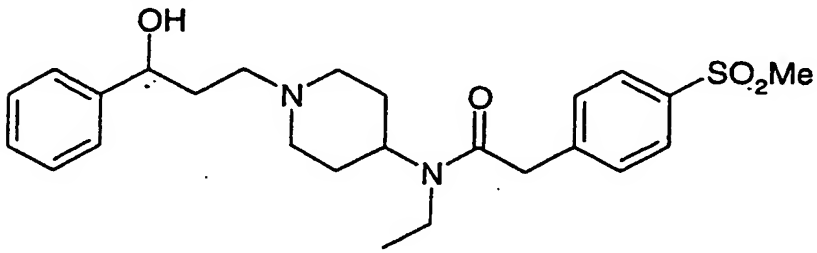
Preparation of *N*-[1-(3-phenyl-3-[4-nitrophenoxycarbonyloxy]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide



To a solution of *N*-[1-(3-phenyl-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 4) (0.50g, 1.1mmol) in DCM (5mL) was added 4-nitrophenylchloroformate (240mg, 1.2mmol) followed by triethylamine (167μL, 1.2mmol). The resulting mixture was stirred at room temperature for 24h then partitioned between DCM and saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated giving the title compound as a gum (645mg, 95%) which was characterised by LC-MS; MS: 624.

Method 4

Preparation of *N*-[1-(3-phenyl-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

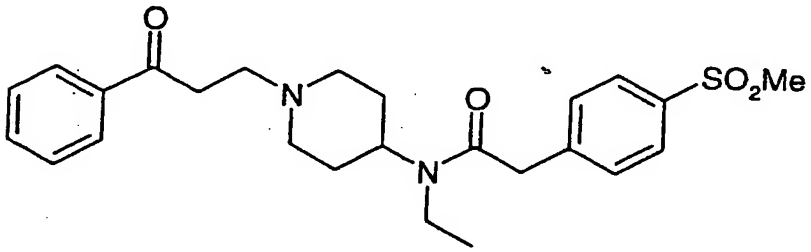


To a solution of *N*-[1-(3-phenyl-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Method 5) (5.00g, 10.1mmol) in methanol

(150mL) was added sodium borohydride (0.96g, 25.4mmol) portionwise. The resulting mixture was stirred at room temperature for 20h. Water (10mL) was added and the mixture was evaporated. The residue was purified by silica column chromatography (gradient elution from ethyl acetate to 50% ethyl acetate/MeOH) to give the title compound (3.92g, 84%); NMR: ($CDCl_3$): 1.14 and 1.23 (t, 3H), 1.56 (m, 1H), 1.75 (m, 2H), 1.83 (m, 3H), 1.98 (m, 1H), 2.20 (m, 1H), 2.56 (m, 1H), 2.66 (m, 1H), 3.02 (s, 3H), 3.10 (m, 1H), 3.18 (m, 1H), 3.31 (q, 2H), 3.57 and 4.49 (m, 1H), 3.79 and 3.80 (s, 2H), 4.94 (m, 1H), 7.23 (m, 1H), 7.34 (m, 4H), 7.44 (d, 2H) and 7.90 (d, 2H); MS: 459.

Method 5

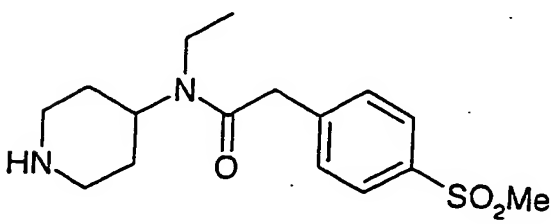
Preparation of *N*-[1-(3-phenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride



To a solution of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 6) (14.8g, 45.8mmol) and DIPEA (24mL, 137mmol) in DMF (250mL) was added 3-chloropropiophenone (7.3g, 43.5mmol). The resulting mixture was stirred at room temperature for 20h. The mixture was evaporated and the residue triturated with 5%MeOH/EtOAc to give a solid which was collected by filtration and washed with EtOAc affording the title compound (16.9g, 75%); NMR (DMSO at 373K): 1.14 (t, 3H), 1.77 (m, 2H), 2.34 (m, 2H), 3.11 (m, 2H), 3.15 (s, 3H), 3.45-3.60 (m, 6H), 3.65 (t, 2H), 3.93 (s, 2H), 4.25 (br m, 1H), 7.53 (m, 4H), 7.65 (m, 1H), 7.84 (d, 2H) and 7.98 (d, 2H); MS: 457.

Method 6

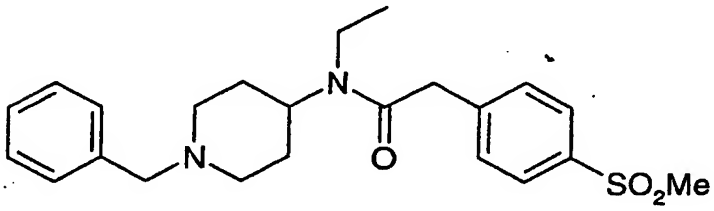
Preparation of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide



To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 7) (34g, 82mmol) in ethanol (600mL) was added ammonium formate (40g). The mixture was purged with argon and 30% Pd on carbon (4.2g) was added. The resulting mixture was stirred at reflux for 4 h, then allowed to cool and filtered through diatomaceous earth. The filtrate was evaporated to give a thick oil which solidified on standing to yield the title compound (24.9 g, 94%); NMR: 1.02 and 1.15 (t, 3H), 1.4 -1.6 (br m, 4H), 2.45 (m, 2H), 2.93 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.32 (q, 2H), 3.72 and 4.18 (m, 1H), 3.80 and 3.87 (s, 2H), 7.50 (m, 2H), 7.85 (m, 2H); MS: 325.

Method 7

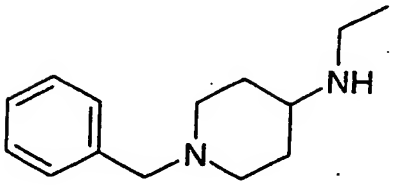
Preparation of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonyl-phenylacetamide



To a solution of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride (Method 8) (32.0g, 110mmol) in DCM (500mL) was DIPEA (60mL) with stirring to ensure complete dissolution. 4-Methanesulfonylphenylacetic acid (25.0g, 117mmol), 4-dimethylamino-pyridine (2.0g) and dicyclohexylcarbodiimide (25.0g, 121mmol) were added and the resulting mixture was stirred at room temperature for 20h. The precipitate was removed by filtration and the resulting solution was washed successively with 2N aqueous HCl, water and 1N aqueous NaOH, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent 10% MeOH/ethyl acetate) to afford the title compound (35g, 76%); NMR: 1.00 and 1.14 (t, 3H), 1.45 and 1.70 (m, 2H), 1.95 (br m, 2H), 2.80 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.33 (q, 2H), 3.45 (s, 2H), 3.80 and 3.87 (s, 2H), 3.70 and 4.10 (m, 1H), 7.2 - 7.3 (m, 5H), 7.48 (m, 2H), 7.82 (m, 2H); MS: 415.

Method 8

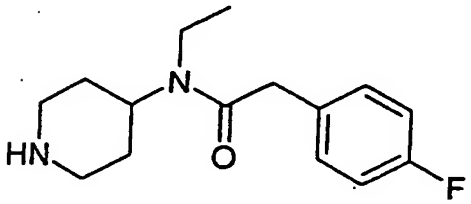
Preparation of phenylmethyl-4-ethylaminopiperidine dihydrochloride



To a solution of 1-phenylmethyl-4-piperidone (25.0g, 132mmol) in THF (250mL) was added ethylamine hydrochloride (12.0g, 147mmol) and methanol (50mL) and the resulting mixture stirred at room temperature for 10min. Sodium triacetoxyborohydride (40g, 189mmol) was added portionwise and the resulting mixture stirred at room temperature for 1h. 2M Sodium hydroxide solution (250mL) was added and the resulting mixture extracted with diethyl ether. The organic extracts were dried (K_2CO_3) and evaporated to give 1-phenylmethyl-4-ethylaminopiperidine as an oil. This was dissolved in ethanol (500mL) and concentrated hydrochloric acid (20mL) was added. The resulting crystals were collected, washed with diethyl ether and dried giving the title compound as a solid (38g); NMR: ($CDCl_3$): 1.10 (t, 3H), 1.40 (m, 2H), 1.83 (m, 2H), 2.02 (m, 2H), 2.65 (q, 2H), 2.85 (m, 2H), 3.50 (s, 2H), 3.75 (m, 1H), 7.2 - 7.4 (m, 5H); MS: 219.

Method 9

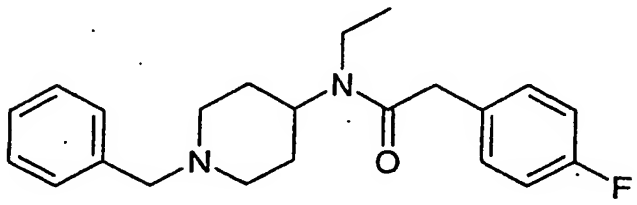
Preparation of *N*-4-piperidinyl-*N*-ethyl-4-fluorophenylacetamide



This was prepared by reacting *N*-(1-phenylmethyl-4-piperidinyl-*N*-ethyl-4-fluorophenylacetamide according to the procedure used for Method 6; NMR (formic acid salt): 0.97 and 1.10 (t, 3H), 1.46 and 1.62 (m, 2H), 1.8 - 2.0 (m, 2H), 2.78 (m, 2H), 3.1 - 3.3 (m, 4H), 3.65 and 3.74 (s, 2H), 3.97 and 4.22 (m, 1H), 7.08 (m, 2H), 7.25 (m, 2H), 8.42 (s, 1H); MS: 265.

Method 10

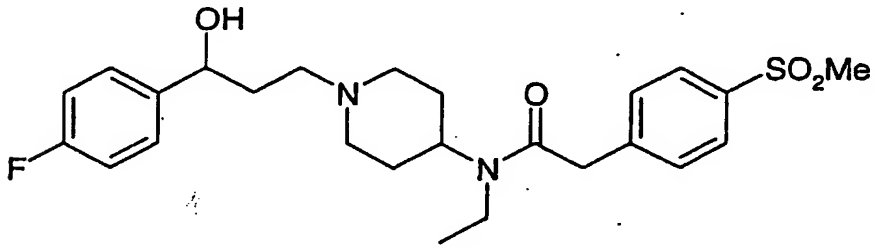
Preparation of *N*-(1-phenylmethyl-4-piperidinyl-*N*-ethyl-4-fluorophenylacetamide



This was prepared by reacting 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride with 4-fluorophenylacetic acid according to the procedure used for Method 7; NMR ($CDCl_3$): 1.13 and 1.19 (t, 3H), 1.35 and 1.85 (m, 2H), 1.74 and 2.08 (m, 2H), 2.90 (br m, 2H), 3.30 (m, 2H), 3.46 (s, 2H), 3.66 (s, 2H), 3.55 and 4.42 (m, 1H), 7.00 (m, 2H), 7.2 - 7.3 (m, 7H); MS: 355.

Method 11

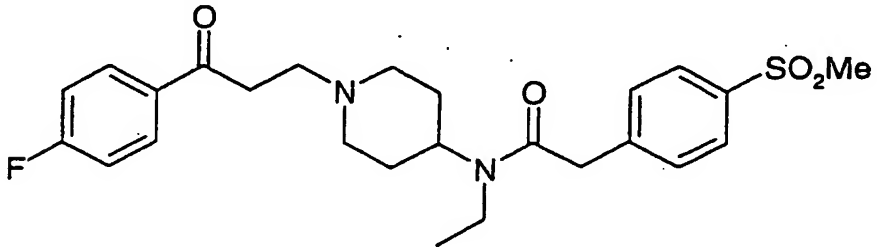
Preparation of *N*-[1-(3-[4-fluorophenyl]-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide



This was prepared by reacting *N*-[1-(3-[4-fluorophenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Method 12) according to the procedure used for Method 4; NMR: MS: 477.

Method 12

Preparation of *N*-[1-(3-[4-fluorophenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride

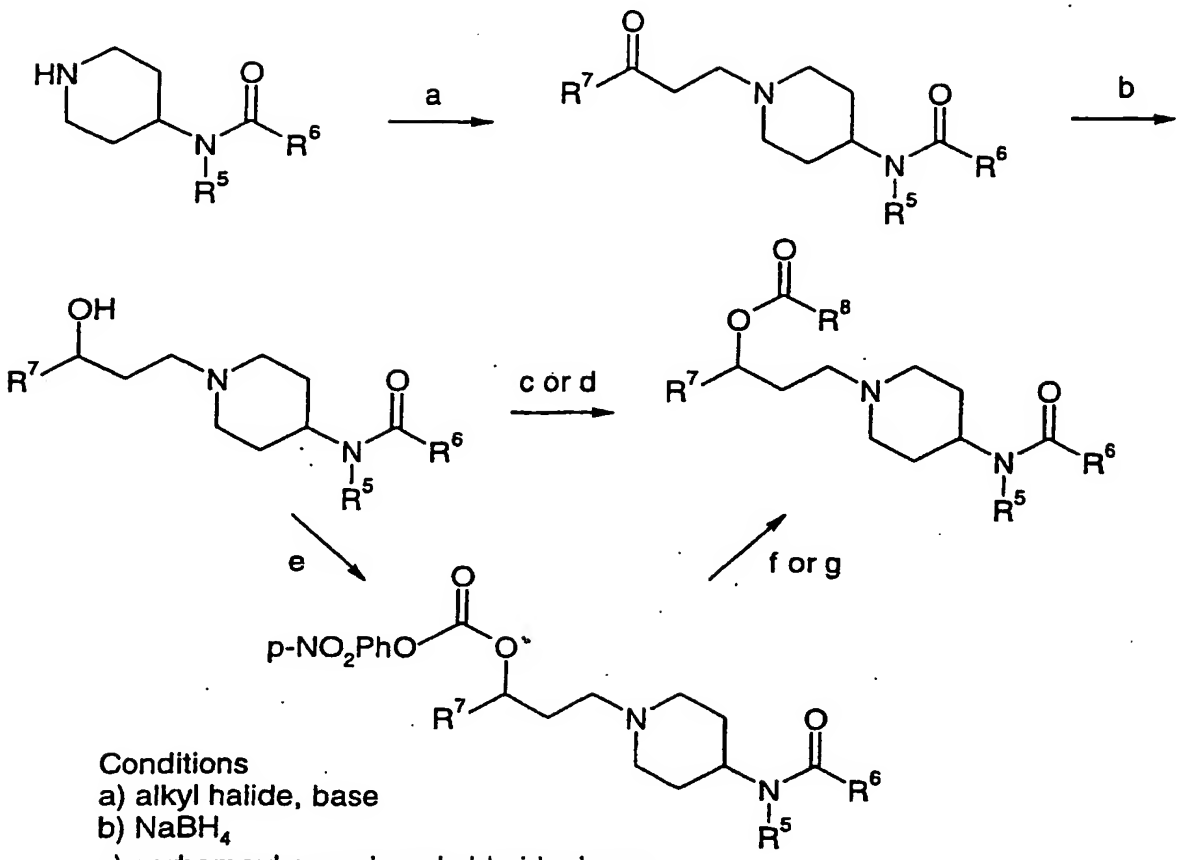


To a solution of *N*-4-piperidinyl-*N*-ethyl-4-methanesulfonylphenylacetamide (Method 6) (1.3g, 4.0mmol) in DMF (25mL) was added DIPEA (2mL, 11.5mmol) and 3-chloro-4'-fluoropropiophenone (770mg, 4.0mmol). The resulting mixture was stirred at room temperature overnight then evaporated. The residue was heated to reflux with 5% methanol in ethyl acetate giving a white solid which was isolated (1.6g, 80%). NMR: 1.00 and 1.16 (t, 3H), 1.75 (t, 2H), 2.23 (q, 2H), 3.10 (t, 2H), 3.18 (s, 3H), 3.30 (m, 2H), 3.35 and 3.64 (q, 2H), 3.56 (m, 2H), 3.82 and 3.93 (s, 2H), 4.15 and 4.28 (m, 1H), 7.40 (m, 2H), 7.50 (m, 2H), 7.83 (m, 2H), 8.07 (m, 2H); MS: 475.

EXAMPLE 6

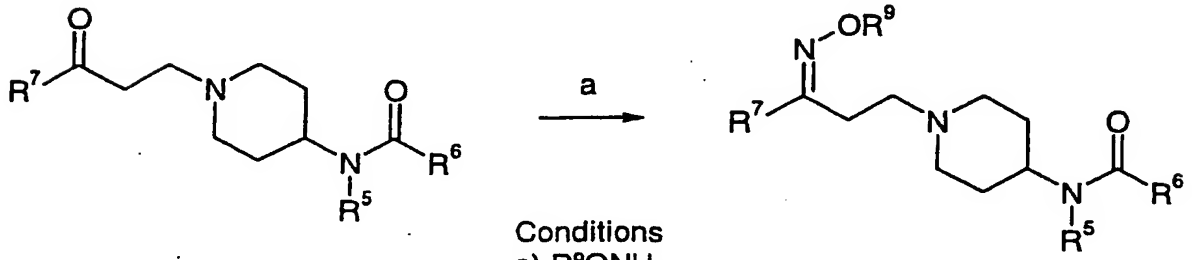
The ability of compounds to inhibit the binding of RANTES or MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES or MIP-1α, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES or MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES or MIP-1α was calculated (IC_{50}). Certain compounds of formula (I) had an IC_{50} of less than 50μM.

SCHEME 1



Conditions
a) alkyl halide, base
b) $NaBH_4$
c) carbamoyl or carbonyl chloride, base
d) isocyanate
e) p-NO_2PhOCOCl, base
f) amine
g) alcohol

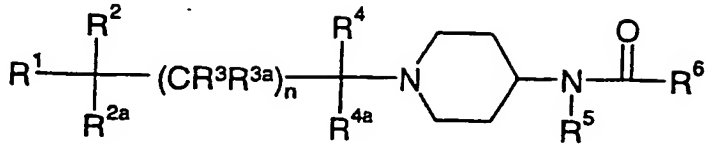
SCHEME 2



Conditions
a) R^9ONH_2

CLAIMS

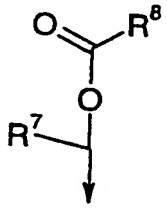
1. A compound of formula (I):

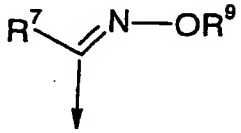


(I)

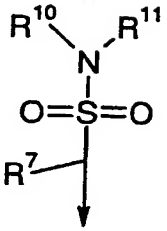
wherein:

R^1 is a group selected from:





and



R^2, R^{2a}, R^4 and R^{4a} are, independently, hydrogen or C_{1-4} alkyl;

R^3 and R^{3a} are, independently, hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

n is 0 or 1;

R^5 is hydrogen, C_{1-4} alkyl (optionally substituted by halogen, hydroxy, C_{1-4} alkoxy, C_{3-7} cycloalkyl, SH, C_{1-4} alkylthio, cyano or $S(O)_q(C_{1-4}$ alkyl)), C_{3-4} alkenyl, C_{3-4} alkynyl or C_{3-7} cycloalkyl;

R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH;

R^7 is phenyl, heteroaryl, phenyl(C_{1-4} alkyl) or heteroaryl(C_{1-4} alkyl);

R^8 is C_{1-8} alkyl, OR^{12}, $NR^{13}R^{14}$, phenyl, heteroaryl, phenyl(C_{1-2})alkyl or heteroaryl(C_{1-2})alkyl;

R^9, R^{10} and R^{11} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy, phenyl or heteroaryl), phenyl or heteroaryl; or R^{10} and R^{11} may join to form a 5- or 6-membered ring which may additionally include an oxygen atom or a further nitrogen atom, said ring being optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl);

R^{12} and R^{13} are C_{1-8} alkyl (optionally substituted by halogen, OH, cyano, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, $NR^{15}R^{16}$, C(O)NH(OH),

NHC(O)(C_{1-4} alkyl), heterocyclyl, phenyl or heteroaryl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl (optionally substituted by C_{1-6} alkyl), phenyl, heteroaryl or heterocyclyl;

R^{14} is hydrogen or is independently selected from the list of options recited for R^{13};

or R^{13} and R^{14} join to form a 5, 6, 7 or 8-membered monocyclic or bicyclic ring system which is optionally unsaturated, optionally includes a further nitrogen atom or also includes an oxygen or sulphur atom, and which is optionally substituted by OH, C_{1-6} alkyl or C_{1-6} hydroxyalkyl;

R^{15} and R^{16} are, independently, hydrogen or C_{1-6} alkyl;

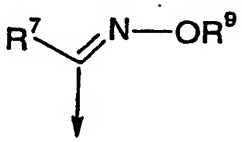
wherein the phenyl, heteroaryl and heterocyclyl rings of any of the foregoing are independently optionally substituted by halo, cyano, nitro, oxo, hydroxy, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^{17}R^{18}$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3;

R^{17} and R^{18} are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or $C(O)(C_{1-4}$ alkyl);

m, p and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof;

provided that when R^1 is



n is 0 or 1; R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^9 are all hydrogen; and R^6 is unsubstituted phenyl; then R^7 is not optionally substituted phenyl, or a salt thereof.

2. A compound of formula (I) as claimed in claim 1 wherein n is 0; R^2, R^{2a} and R^4 are all hydrogen; and R^{4a} is hydrogen or methyl.

3. A compound of formula (I) as claimed in claim 1 wherein n is 1; R^2, R^{2a}, R^3, R^{3a} and R^4 are all hydrogen; and R^{4a} is hydrogen or methyl.

4. A compound as claimed in claim 1, 2 or 3 wherein R^5 is methyl, ethyl or allyl.

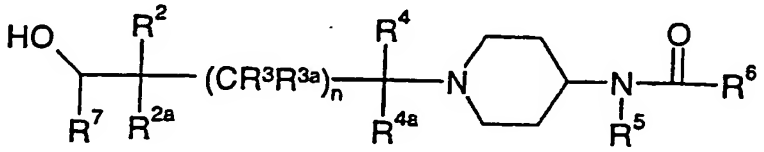
5. A compound as claimed in claim 1, 2, 3 or 4 wherein R^6 is benzyl singly substituted by $S(O)_2(C_{1-4})$alkyl or $S(O)_2NR^9R^{10}$; wherein R^9 and R^{10} are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or $C(O)(C_{1-4}$ alkyl).

6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein R^7 is phenyl optionally substituted by halo, cyano, methyl, ethyl, methoxy, ethoxy, NH_2, $NHCH_3$, $N(CH_3)_2$, CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3.

7. A compound as claimed in claim 1, 2, 3, 4, 5 or 6 wherein R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, $NR^{13}R^{14}$, C_{3-7} cycloalkyl (optionally substituted by C_{1-4} alkyl) or heteroaryl; R^{13} is C_{1-8} alkyl (optionally substituted by halogen, cyano, hydroxy, NH_2, $N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, C_{1-4} thioalkyl, C_{3-7} cycloalkyl, heterocyclyl, phenyl, heteroaryl, $NHC(O)(C_{1-4}$ alkyl) or C(O)NHOH), C_{3-6} alkenyl, C_{3-6} alkynyl, phenyl or heteroaryl; R^{14} is hydrogen, C_{1-8} alkyl (optionally substituted by cyano or hydroxy) or C_{3-6} alkenyl; or R^{13} and R^{14} together with the nitrogen to which hey are attached form a oxiranyl, pyrrolidinyl, piperidinyl, morpholinyl, dihydropyrrolyl, tetrahydropyridinyl, piperazinyl, thiomorpholinyl, homopiperazinyl or homopiperidinyl ring all of which are optionally substituted by hydroxy, C_{1-4} alkyl or C_{1-4} hydroxyalkyl; wherein phenyl is optionally substituted by halogen, cyano, hydroxy or C_{1-6} alkyl; and heteroaryl is optionally substituted by oxo, halogen, cyano, hydroxy or C_{1-6} alkyl.

8. A compound as claimed in claim 1, 2, 3, 4, 5, 6 or 7 wherein R^9 is C_{1-4} alkyl or C_{3-4} alkenyl.

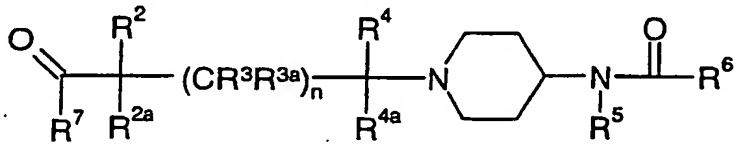
9. A processes for the preparation of a compound of formula (I) as claimed in claim 1 wherein R^1 is $CHR^7OC(O)R^8$ comprising reacting a compound of formula (II):



(II)

with a compound of formula $R^8C(O)Cl$ in the presence of a suitable base and in a suitable solvent.

10. A processes for the preparation of a compound of formula (I) as claimed in claim 1 wherein R^1 is $CR^7{=}NOR^9$ comprising reacting a compound of formula (III):



(III)

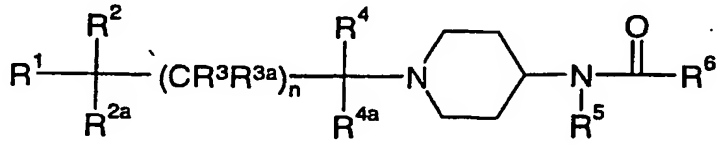
with a compound of formula R^9ONH_2 in a suitable solvent.

11. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 8, and a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 8, for use in therapy.

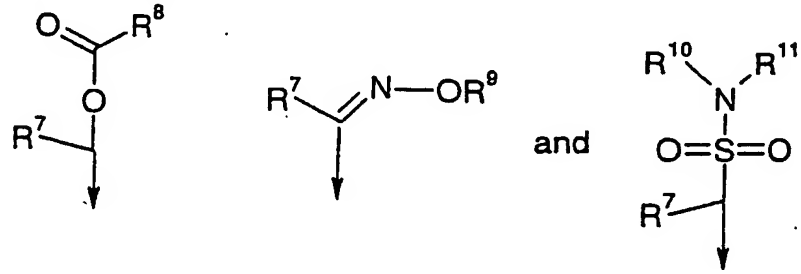
13. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 8, in the manufacture of a medicament for use in therapy.

14. A compound of the formula (I):



(I)

wherein: R^1 is a group selected from:



and

R^2, R^{2a}, R^4 and R^{4a} are, independently, hydrogen or C_{1-4} alkyl;

R^3 and R^{3a} are, independently, hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

n is 0 or 1;

R^5 is hydrogen, C_{1-4} alkyl (optionally substituted by halogen, hydroxy, C_{1-4} alkoxy, C_{3-7} cycloalkyl, SH, C_{1-4} alkylthio, cyano or $S(O)_q(C_{1-4}$ alkyl)), C_{3-4} alkenyl, C_{3-4} alkynyl or C_{3-7} cycloalkyl;

R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH;

R^7 is phenyl, heteroaryl, phenyl(C_{1-4} alkyl) or heteroaryl(C_{1-4} alkyl);

R^8 is C_{1-8} alkyl, OR^{12}, $NR^{13}R^{14}$, phenyl, heteroaryl, phenyl(C_{1-2})alkyl or heteroaryl(C_{1-2})alkyl;

R^9, R^{10} and R^{11} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy, phenyl or heteroaryl), phenyl or heteroaryl; or R^{10} and R^{11} may join to form a 5- or 6-membered ring which may additionally include an oxygen atom or a further nitrogen atom, said ring being optionally substituted with C_{1-4} alkyl, C(O)H or $C(O)(C_{1-4}$ alkyl);

R^{12} and R^{13} are C_{1-8} alkyl (optionally substituted by halogen, OH, cyano, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, $NR^{15}R^{16}$, C(O)NH(OH), $NHC(O)(C_{1-4}$ alkyl), heterocyclyl, phenyl or heteroaryl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl (optionally substituted by C_{1-6} alkyl), phenyl, heteroaryl or heterocyclyl;

R^{14} is hydrogen or is independently selected from the list of options recited for R^{13}; or R^{13} and R^{14} join to form a 5, 6, 7 or 8-membered monocyclic or bicyclic ring system which is optionally unsaturated, optionally includes a further nitrogen atom or also includes an oxygen or sulphur atom, and which is optionally substituted by OH, C_{1-6} alkyl or C_{1-6} hydroxyalkyl;

R^{15} and R^{16} are, independently, hydrogen or C_{1-6} alkyl;

wherein the phenyl, heteroaryl and heterocyclyl rings of any of the foregoing are independently optionally substituted by halo, cyano, nitro, oxo, hydroxy, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^{17}R^{18}$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3;

R^{17} and R^{18} are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or C(O)(C_{1-4} alkyl);

m, p and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof; for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

15. A method of treating a chemokine mediated disease state in a warm blooded animal suffering from, or at risk of, said disease, which comprises administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 8, or as defined in claim 14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00598

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/58, C07D 401/12, C07D 405/12, C07D 413/12, C07D 417/12, A61K 31/4468, A61K 31/4523, A61P 11/00, A61P 17/00, A61P 29/00, A61P 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA, EPO-INTERNAL, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0903349 A2 (F. HOFFMANN-LA ROCHE AG), 24 March 1999 (24.03.99) --	1-15
X	EP 1013276 A1 (PFIZER INC.), 28 June 2000 (28.06.00) --	1-15
X	WO 9964394 A1 (SCHERING CORPORATION), 16 December 1999 (16.12.99) --	1-15
X	WO 9634857 A1 (SCHERING CORPORATION), 7 November 1996 (07.11.96) --	1-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2002	05 -07- 2002
Name and mailing address of the ISA: Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer VIVECA NORÉN/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00598

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0192227 A1 (ASTRAZENECA AB), 6 December 2001 (06.12.01) ---	1-15
A	GB 1538542 A (JOHN WYETH & BROTHER LIMITED), 24 January 1979 (24.01.79) --- --------	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00598

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 15 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 02/00598

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 02/00598

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		NZ 307715 A	28/01/00
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		US 5840725 A	24/11/98
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